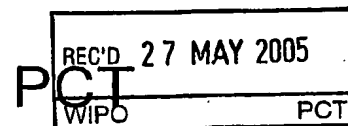


# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION See paragraph 2 below

International application No.  
PCT/US2005/000020

International filing date (day/month/year)  
18.01.2005

Priority date (day/month/year)  
22.01.2004

International Patent Classification (IPC) or both national classification and IPC  
C07D295/08, C07D311/78, C07D335/04, C07D221/18, A61K31/4453, A61K31/4523, A61K31/55, A61P15/12

Applicant  
ELI LILLY AND COMPANY

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the International application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Tel. +49 89 2399 - 0 Tx: 523658 epmu d  
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Authorized Officer

Kollmannsberger, M

Telephone No. +49 89 2399-7364



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15

because:

☒ the said international application, or the said claims Nos. 15 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, Inventive step or  
Industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	29-36
	No: Claims	1-28
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	1-14,16-36
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

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**Box No. VI Certain documents cited**

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**1. Certain published documents (Rules 43bis.1 and 70.10)**

**and / or**

**2. Non-written disclosures (Rules 43bis.1 and 70.9)**

**see form 210**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/000020

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V-1. State of the art:**

The following documents are considered relevant:

- D1: WO 2004/009086 A (ELI LILLY AND COMPANY; DALLY, ROBERT, DEAN; DODGE, JEFFREY, ALAN; FRAN) 29 January 2004 (2004-01-29)
- D2: EP-A-0 826 679 (ELI LILLY AND COMPANY) 4 March 1998 (1998-03-04)
- D3: EP-A-0 761 669 (ELI LILLY AND COMPANY) 12 March 1997 (1997-03-12)
- D4: EP-A-0 895 989 (ELI LILLY AND COMPANY) 10 February 1999 (1999-02-10)
- D5: US-A-5 567 712 (PALKOWITZ ET AL) 22 October 1996 (1996-10-22)
- D6: EP-A-0 835 868 (ELI LILLY AND COMPANY) 15 April 1998 (1998-04-15)
- D7: EP-A-0 835 867 (ELI LILLY AND COMPANY) 15 April 1998 (1998-04-15)

D1 is a P-document and will be disregarded during the PCT procedure.

**V-2. Novelty (Art. 33(2) PCT):**

D2 discloses compounds (see claim 1) which largely overlap with the compounds claimed in present claims 1-28 for X=O (see definitions of R1-R5 in claim 1 of D2). Fluoro substituents at the phenyl ring are specifically mentioned. Although D2 does not

disclose example compounds in the overlapping range, there is no new technical (i. e. structural) teaching apparent which would confer novelty to the claimed overlap in the sense of a novel selection.

D3 discloses compounds (see structure (I) in claim 1) which largely overlap with the compounds claimed in present claims 1-28 in case R6 and X1 combine to form a cycle (see definitions of R1-R4 in claim 1 of D2). Fluoro substituents at the phenyl ring are specifically mentioned. Although D2 does not disclose example compounds in the overlapping range, there is no new technical (structural) teaching apparent which would confer novelty to the claimed overlap in the sense of a novel selection.

Since D2 and D3 concern the treatment of menopause syndrome, also claims 15 and 16 are not novel. Hot flashes are not specifically mentioned in D2/D3 so claim 17 is considered a novel selection from these documents.

The claims are novel over D4, D5 and D6 on account of the fluoro substituent at the phenyl ring which is absent in D4 and not specifically disclosed in D5/D6. The claims are novel over D7 due to the spacer X which cannot be a heteroatom in D7.

Claims 29-36 are novel over the cited documents on account of the carbon spacer between the naphthalene and the phenyl ring.

**V-3. Inventive step (Art. 33(3) PCT):**

The present application deals with compounds being selective estrogen receptor ligands useful in the treatment of symptoms affecting women around menopause.

All of D2-D7 deal with the same problem, i. e. compounds having this activity. Any of them could be regarded as closest state of the art.

As far as the subject-matter of the claims is novel, it represents an obvious solution of the problem of finding further compounds having the claimed activity. The compounds of D4 (see claims), D6 (which specifically mentions hot flashes, see page 5 line 37; see

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/000020

compounds defined in the claims) or D6 (see e. g. examples 4, 5) differ only in the absence of the fluoro substituent at the phenyl ring. From e. g. D2, and D3 as well as from D6 and D7 it is however clear that the fluoro substituent is an alternative to hydrogen or O-bound substituents at this position (see e. g. definitions of R2/R3 in D6 and D7). It is noted that e. g. the compound disclosed in D7, page 6 line 54 has a fluoro substituent at the relevant position and differs from the present claims only in the spacer X.

The problem to be solved must be seen in the provision of compounds unexpectedly showing advantageous effects compared to the structurally closest compounds of the prior art. Since no biological data is on file it is not apparent that such a problem has been solved.

Concerning the intermediates of claims 18-36 an inventive step could only be acknowledged in connection with inventive end products.

**Re Item VI**

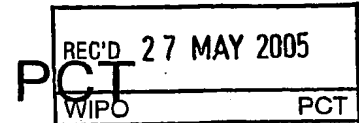
**Certain documents cited**

**Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO20040090086	29.01.2004	16.07.2003	22.07.2003

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION See paragraph 2 below

International application No.  
PCT/US2005/000020

International filing date (day/month/year)  
18.01.2005

Priority date (day/month/year)  
22.01.2004

International Patent Classification (IPC) or both national classification and IPC  
C07D295/08, C07D311/78, C07D335/04, C07D221/18, A61K31/4453, A61K31/4523, A61K31/55, A61P15/12

Applicant  
ELI LILLY AND COMPANY

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Fax: +49 89 2399 - 4465

Authorized Officer

Kollmannsberger, M

Telephone No. +49 89 2399-7364





**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

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**Box No. I Basis of the opinion**

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1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

---

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15

because:

☒ the said international application, or the said claims Nos. 15 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000020

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	29-36
	No: Claims	1-28
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	1-14,16-36
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

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**Box No. VI Certain documents cited**

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**1. Certain published documents (Rules 43bis.1 and 70.10)**

**and / or**

**2. Non-written disclosures (Rules 43bis.1 and 70.9)**

**see form 210**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/000020

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V-1. State of the art:**

The following documents are considered relevant:

- D1: WO 2004/009086 A (ELI LILLY AND COMPANY; DALLY, ROBERT, DEAN; DODGE, JEFFREY, ALAN; FRAN) 29 January 2004 (2004-01-29)
- D2: EP-A-0 826 679 (ELI LILLY AND COMPANY) 4 March 1998 (1998-03-04)
- D3: EP-A-0 761 669 (ELI LILLY AND COMPANY) 12 March 1997 (1997-03-12)
- D4: EP-A-0 895 989 (ELI LILLY AND COMPANY) 10 February 1999 (1999-02-10)
- D5: US-A-5 567 712 (PALKOWITZ ET AL) 22 October 1996 (1996-10-22)
- D6: EP-A-0 835 868 (ELI LILLY AND COMPANY) 15 April 1998 (1998-04-15)
- D7: EP-A-0 835 867 (ELI LILLY AND COMPANY) 15 April 1998 (1998-04-15)

D1 is a P-document and will be disregarded during the PCT procedure.

**V-2. Novelty (Art. 33(2) PCT):**

D2 discloses compounds (see claim 1) which largely overlap with the compounds claimed in present claims 1-28 for X=O (see definitions of R1-R5 in claim 1 of D2). Fluoro substituents at the phenyl ring are specifically mentioned. Although D2 does not

disclose example compounds in the overlapping range, there is no new technical (i. e. structural) teaching apparent which would confer novelty to the claimed overlap in the sense of a novel selection.

D3 discloses compounds (see structure (I) in claim 1) which largely overlap with the compounds claimed in present claims 1-28 in case R6 and X1 combine to form a cycle (see definitions of R1-R4 in claim 1 of D2). Fluoro substituents at the phenyl ring are specifically mentioned. Although D2 does not disclose example compounds in the overlapping range, there is no new technical (structural) teaching apparent which would confer novelty to the claimed overlap in the sense of a novel selection.

Since D2 and D3 concern the treatment of menopause syndrome, also claims 15 and 16 are not novel. Hot flashes are not specifically mentioned in D2/D3 so claim 17 is considered a novel selection from these documents.

The claims are novel over D4, D5 and D6 on account of the fluoro substituent at the phenyl ring which is absent in D4 and not specifically disclosed in D5/D6. The claims are novel over D7 due to the spacer X which cannot be a heteroatom in D7.

Claims 29-36 are novel over the cited documents on account of the carbon spacer between the naphthalene and the phenyl ring.

**V-3. Inventive step (Art. 33(3) PCT):**

The present application deals with compounds being selective estrogen receptor ligands useful in the treatment of symptoms affecting women around menopause.

All of D2-D7 deal with the same problem, i. e. compounds having this activity. Any of them could be regarded as closest state of the art.

As far as the subject-matter of the claims is novel, it represents an obvious solution of the problem of finding further compounds having the claimed activity. The compounds of D4 (see claims), D6 (which specifically mentions hot flashes, see page 5 line 37; see

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/000020

compounds defined in the claims) or D6 (see e. g. examples 4, 5) differ only in the absence of the fluoro substituent at the phenyl ring. From e. g. D2, and D3 as well as from D6 and D7 it is however clear that the fluoro substituent is an alternative to hydrogen or O-bound substituents at this position (see e. g. definitions of R2/R3 in D6 and D7). It is noted that e. g. the compound disclosed in D7, page 6 line 54 has a fluoro substituent at the relevant position and differs from the present claims only in the spacer X.

The problem to be solved must be seen in the provision of compounds unexpectedly showing advantageous effects compared to the structurally closest compounds of the prior art. Since no biological data is on file it is not apparent that such a problem has been solved.

Concerning the intermediates of claims 18-36 an inventive step could only be acknowledged in connection with inventive end products.

**Re Item VI**

**Certain documents cited**

**Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO20040090086	29.01.2004	16.07.2003	22.07.2003